REMARKS

Status of the Claims

Claims 1-30, 32-34 and 47 were pending. Claims 16-30, 32-34 and 47 were withdrawn by the Examiner as drawn to a non-elected invention. Claims 16-30, 32-34 and 47 are canceled herein without prejudice or disclaimer. Applicant reserves the right to prosecute the canceled subject matter in a divisional or continuation application. New claims 58-68 are added herein. Claims 1-15 and 58-68 are presently pending.

Claim Amendments

For convenience, all citations to the Specification below refer to the published Specification (Publ. No. 20050287604).

Claim 1 is amended to add the step of obtaining a sample of maternal blood that contains one or more fetal cells and to clarify that the maternal antibody that is detected is bound to a paternally inherited fetal antigen on a fetal cell. The amendment is supported at least in FIG. 1 and FIG. 2, original claim 5 and in the Specification at least in the Abstract and Paragraphs [0004]-[0006].

New claim 58 is added to recite the method of claim 1, further comprising the steps of "isolating a fraction comprising peripheral blood mononuclear cells from the sample," "contacting fetal cells bound to maternal antibodies with an agent capable of forming a complex with maternal antibodies," and "recovering fetal cells bound to agent-maternal antibody complexes." The new claim is supported at least in original claim 16 and 23-27, FIG. 1 and FIG. 2 and in the Specification in the Abstract and Paragraphs [0034]. The Abstract states that, "The present invention provides methods for identifying and/or enriching fetal cells" (emphasis added) making it clear that methods of identification and methods of enriching fetal cells are not mutually exclusive, but may be performed concurrently or consecutively. Original claims 23-27 specifically recited methods of enriching fetal cells by contacting fetal cells bound to maternal antibodies with a detectable or isolatable agent capable of forming a complex with maternal antibodies. In original claim 25, the fetal cells are enriched by a method comprising detecting the label (by necessity detecting the labeled fetal cells) and separating a fraction comprising the label. In original claim 26, the agent was fluorescently labeled and the enrichment comprised performing fluorescence activated cell sorting to recover cells bound by agent-maternal antibody complexes. Example 1

gives a detailed protocol for enriching fetal cells in which the step of detecting maternal antibodies bound to fetal cells is an integral part of the method of enriching fetal cells by FACS. Thus, it is clear from the Specification, Figures and original claims that detection and enrichment of fetal cells may be performed using the same agents and identical or overlapping steps in the claimed methods. Applicant respectfully submit that new claims 58-69, which depend from claim 1, should be properly examined with claims 1-15.

New claim 59 recites the method of claim 58, further comprising adding maternal antibodies against a paternally inherited fetal antigen to the isolated peripheral blood mononuclear cells under conditions that allow the maternal antibodies to bind to the fetal cells. The new claim is supported by FIG. 1 and in the Specification at least at Paragraphs [0008], [0016], [0036]-[0044] and [0060]-[0062].

New claim 60 recites the method of claim 59, further comprising depleting the peripheral blood mononuclear cells of at least one type of maternal cell. The new claim is supported by original claim 19 and in the Specification at least at Paragraphs [0010] and [0120]-[0125].

New claim 61 is added to recite the method of claim 59, wherein the maternal antibodies against a paternally inherited fetal antigen are obtained from the blood of the same individual as the maternal blood sample. The amendment is supported in FIG 1 and the Specification at least at Paragraphs [0031], [0036]-[0044], [0047]-[0049] and [0052]-[0054].

New claim 62 is added to recite the method of claim 59, wherein the peripheral blood mononuclear cells are cultured in vitro before the maternal antibodies are added. The new claim is supported at least by original claim 22 and in the Specification at least at Paragraph [0134].

New claim 63 is added to recite the method of claim 58, wherein the agent is bound to a detectable label or isolatable label. The amendment is supported in original claim 23, FIG. 2 and in the Specification at least at Paragraphs [0017] and [0105]-[0111] and Example 1.

New claim 64 is added to recite the method of claim 63, wherein the detectable or isolatable label is selected from the group consisting of a fluorescent label, a radioactive label, a paramagnetic particle, a chemoluminescent label, an enzymatic label, and a label that is detectable by virtue of binding to a molecule. The new claim is supported at least by original

claim 24 as well as in the Specification at least at Paragraphs [0017] and [0105]-[0111] and Example 1.

New claim 65 is added to recite the method of claim 63, wherein the step of recovering fetal cells bound to agent-maternal antibody complexes comprises detecting the label and separating a fraction comprising the label. The new claim is supported by original claim 25 and in the Specification at least in Example 1.

New claim 66 is added to recite the method of claim 65, wherein the label is a fluorescent label and the step of recovering cells bound by agent-maternal antibody complexes comprises performing fluorescence activated cell sorting. The new claim is supported by original claim 26 and in the Specification at least at Example 1.

New claim 67 is added to recite the method of claim 65, wherein the label is a paramagnetic particle and the step of recovering cells bound by agent-maternal antibody complexes comprises exposing the cells bound by agent-maternal antibody complexes to a magnet. The new claim is supported by original claim 27 and in the Specification at least at Paragraphs [0010], [0080], [0106], [0114], [0115] and [0117].

New claim 66 is added to recite the method of claim 58, wherein the agent is an antibody or fragment of an antibody. The new claim is supported by original claim 28 and in the Specification at least at Paragraph [0084].

Applicant respectfully submits that no new matter is added by amendment.

Rejection of Claims Under 35 U.S.C. 112, 2nd Paragraph

Claims 1-4 were rejected under 35 U.S.C. 112, 2nd paragraph as indefinite. The Action asserts that "it is unclear how 'maternal antibody bound to a fetal cell' because it is unclear how a maternal antibody would have binding specificity to a fetal cell, i.e. fetal cell antigen."

Applicant does not entirely understand the rejection. The basis for how maternal antibodies would have binding specificity to paternally inherited fetal cell antigens appears to be spelled out explicitly in the Specification at Paragraphs [0005]-[0007]. It is basic textbook

genetics that a given fetus will inherit roughly half its expressed antigens from the paternal genetic donor and half from the maternal side. The paternally inherited fetal cell antigens would not be self-antigens from the perspective of the maternal immune system and could be expected to induce an antibody-based immune system response. Among other things, this is the basis for the very well known phenomenon of Rh disease in newborns, caused by immune system incompatibility between fetal red blood cell antigens and the maternal immune system. Nevertheless, to further clarify the subject matter claim 1 is amended to recite that the maternal antibodies bind to paternally inherited fetal antigens on the fetal cells. Applicant submits that the meaning of amended claim 1 would be clear to the skilled artisan. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims Under 35 U.S.C. 102

Claims 5, 7-9 and 11-13 are rejected as anticipated by Warwick et al. (Detection strategy for maternal antibodies against paternal HPA-1 antigen, Lancet 344:64, 1994, hereafter "Warwick"). Warwick is asserted to "teach a method of identifying fetal cells (platelets) present in sample (amniotic fluid) to determine fetal cell susceptibility to maternal antibodies. In practice, the fetal cells in the sample are exposed to maternal antibodies, whereupon maternal antibodies that bound to the fetal cells which form fetal cell-maternal antibody complexes, are detected and identified. The maternal antibodies comprise maternally produced antibodies specific for paternal HPA-1 antigens, which are paternally-inherited fetal antigens."

Applicant traverses the rejection and respectfully suggests that nowhere does Warwick disclose exposure and binding of fetal cells to maternal antibodies. Warwick refers to an earlier publication by Montemagno et al. who were asserted to "describe 2 cases of severe fetal hydrocephalus that were shown by fetal blood sampling to be caused by thrombocytopenia." However, there is no mention of any use of maternal antibodies bound to fetal cells. Thrombocytopenia refers to an abnormal decrease in blood platelets and would presumably be determined by cell counting, not by use of maternal antibodies. Warwick goes on to say that, "The mothers of both infants were HPA-1a negative and had high concentrations of HPA-1a antibodies that strongly cross-reacted with their partner's platelets." (emphasis added) Applicant notes that in this context, "partner" would refer to the mother's spouse, not to the fetus.

Warwick actually teaches away from the instant claimed methods by suggesting, "an alternative strategy, which is to type each parent for HPA-1 by serological platelet immunofluorescence testing or by polymerase chain reaction DNA techniques. Maternal antibodies directed towards antigens present on paternal platelets can be demonstrated by cross-matching techniques..." (emphasis added) That is, Warwick would lead the skilled artisan to apply the maternal antibodies to paternal platelets, not to identify fetal cells using maternal antibodies. In fact, Warwick appears to teach that the claimed methods should not be used, stating that, "the diagnostic strategy suggested [by Montemagno] is invasive and potentially dangerous if the fetus is profoundly thrombocytopenic and compatible platelets are not available. This is especially relevant in those in whom the fetus has not yet been damaged by maternal antiplatelet antibodies." Thus, Warwick leads the skilled artisan to believe that direct application of maternal antibodies to fetal cells would be invasive and dangerous.

Warwick goes on to suggest that, "Fetal susceptibility to maternal antibodies can be demonstrated by HPA-1 typing of the fetus from amniotic fluid." However, there is no indication that maternal antibodies would be used for such typing. Instead, HPA-1 typing of the fetus would normally be performed using standard (non-maternal) known HPA-1 type-specific antibodies. Thus, Warwick provides no suggestion to directly apply maternal antibodies to fetal cells to identify or enrich the fetal cells, and actually teaches away from the claimed methods.

Rejection of claims under 35 U.S.C. 102 is improper unless each and every element of the claimed subject matter is disclosed in a single prior art reference. Since Warwick discloses HPA-1 typing of parental platelets, and not the use of maternal antibodies to detect or enrich fetal cells by forming maternal antibody-fetal cell complexes, Warwick fails to disclose each element of amended claim 5 and rejection of the claims over Warwick is improper.

Claims 5, 7-9 and 11-13 are rejected under 35 U.S.C. 102(b) over Bussel et al. (NEJM 319:1374-78, 1988, hereafter "Bussel"). The Action states that Bussel et al., "teach that neonatal and fetal alloimmune thrombocytopenia results from the formation of a maternal antibody to paternal antigen, usually PLA1, on fetal cells (platelets) (see Abstract). In practice, the fetal cells from (amniotic fluid sample or cord blood sample) are exposed to maternal antibodies (IgG, IgA,

and IgM), whereupon maternal antibodies that bound to the fetal cells which form fetal cell-maternal antibody complexes, are detected and identified."

Applicant respectfully traverses the rejection and suggests that the characterization above finds little support in the cited publication. First, the study of Bussel was concerned with the effects of administration of gamma globulin and/or dexamethasone administration to the pregnant mother on fetal platelet count. Bussel discloses at page 1375, column 1, first full paragraph that, "Platelet counts were determined in the mothers and fetuses with a Coulter counter." (emphasis added) It is well known in the art that Coulter counters are used in combination with light microscopy to count cells. There is no use of the Coulter counter to detect maternal antibodies bound to fetal cells, and no disclosure in Bussel of the detection of maternal antibodies bound to a paternally inherited fetal antigen on a fetal cell.

While Bussel does disclose at page 1375, column 1, second full paragraph that concentrations of IgG, IgA, and IgM in the mothers and fetuses were measured, nowhere does Bussel state that the IgG, IgA and IgM were bound to fetal cells. The general determination of serum Ig subtype concentrations bears no relationship to the claimed methods.

Bussel than states at page 1375, column 1, third full paragraph that, "Platelet typing studies were performed on platelets from both parents.... A subject was classified as homozygous or heterozygous for a PLA phenotype according to the reaction with antiserum specific for PLA1 and PLA2. Maternal serum samples were tested for the presence of platelet-reactive antibody to paternal as well as to normal target platelets of known PLA and Bak phenotypes..." (emphasis added) In other words, PLA typing was performed using known, standard anti-PLA1 and PLA2 typing antibodies, not maternal antibodies. Further, use of maternal serum samples were tested against paternal platelets and normal target platelets of known phenotype (i.e. standard samples), not against fetal platelets.

The Action makes much of the statement in Bussel's Abstract that, "Neonatal alloimmune thrombocytopenia results from the formation of a maternal antibody to a paternal antigen on fetal platelets." However, this is a statement of the causative mechanism of a disease process, not a description of any method steps performed by the authors. Applicant reiterates

that there is no discussion in Bussel of any method involving detection of maternal antibodies bound to fetal cells to identify or enrich fetal cells. If the Examiner believes that such a teaching exists in Bussel, it is requested that the supporting statement be identified with particularity.

Since Bussel fails to disclose each element of the claimed subject matter, specifically the step of detecting a maternal antibody bound to a paternally inherited fetal antigen on a fetal cell, rejection under 35 U.S.C. 102 is improper. Reconsideration and withdrawal of the rejections is respectfully requested.

Rejection of Claims Under 35 U.S.C. 103

The Action asserts that, "This application currently names joint inventors." Applicant is unaware of any named inventor other than Ralph M. Bohmer. Clarification is requested.

Claims 1-5, 7-9 and 11-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Simons (US Pat. No. 5,447,842, hereafter "Simons") in view of Warwick or Bussel. The Action asserts that, "Simons teaches a method for selectively recovering fetal cells from maternal blood sample...based on differential reactivities of the cells to antibodies specific for polymorphic cell surface antigens, particularly HLA antigens." The Action acknowledges that, "Simons differs from the instant invention in failing to teach that the antibodies that bound to fetal cells are specific for paternally-inherited fetal antigens (present in the fetal cells) are maternal antibodies." However, the Action asserts that it would have been obvious to incorporate the teaching of Warwick or Bussel of maternal antibodies specific for paternally-inherited fetal antigens into the method of Simons, "because Simons specifically recognized and showed the advantage of cell surface antigen specificity of antibodies in separating specific rare cells from a sample, and Warwick or Bussel suggested that maternal antibodies can be used to bind specific rare fetal cells."

Under MPEP 2145, "the claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose." Applicant respectfully submits that the combination of Simons with Warwick or Bussel would in fact change the principle of operation of the primary (Simons) reference. The principal is expressed at multiple points in Simons. For example, the Simons Abstract states that, "In particular, the fetal and maternal cells are separated based on the **non-reactivity** of the fetal cells to an antibody specific for

a cell surface antigen encoded by a **non-transmitted maternal allele**." (emphasis added) Claim 1 of Simons explicitly recites the step of "c. separating maternal cells bound to said first antibody and said second antibody from fetal cells which are bound to one antibody or are non-bound." (emphasis added) Simons reiterates at Col. 3, lines 9-16 that, "The method separates maternal and fetal cells based on differential reactivities of the cells to antibodies specific for polymorphic cell surface antigens, particularly the HLA antigens. In particular, the fetal and maternal cells are separated based on the non-reactivity of the fetal cells to an antibody specific for a cell surface antigen encoded by a nontransmitted maternal allele." (emphasis added) At Col. 3, lines 27-30 Simons recites that, "Fifty percent of the time, the [maternal] allele encoding the antigen is not transmitted and maternal cells bound to the antibody can be separated from non-bound fetal cells." (emphasis added) At Col. 4, lines 15-20, "For HLA loci (or any other polymorphic genetic loci), the fetus inherits one allele for an HLA locus from the mother. The non-reactivity of fetal cells with an antibody specific for the antigen expressed by the nontransmitted allele can be used to separate fetal and maternal cells." (emphasis added) Most tellingly, at Col. 5, lines 30-36 Simons states that,

> **The method also does not attempt to distinguish the fetal cells based on "fetal" antigens** such as fetal hemoglobin which may also be expressed by some maternal cells. **In the present method, rather than selecting a fetal antigen that is present on some maternal cells (oncofetal antigens), the method utilizes a maternal antigen which is not present on any fetal cells**. Once an antibody that does not react with some cells in the sample is identified, all of the cells which **do not react with the antibody** are fetal cells. Furthermore, all nucleated fetal cells that express HLA antigens fail to react with the antibody because the HLA antigen is not transmitted to that fetus. The lack of reactivity is not related to a particular fetal stage of development or to a particular fetal cell type. **Therefore all non-reactive cells are fetal cells.** (emphasis added)

Thus, the entire principle of operation taught by Simons is completely opposite from that of the instant method. In Simons, the separation depended upon the non-reactivity of fetal cells to antibodies that bound specifically to maternal antigens. In the instant methods, the separation (or identification) depends explicitly on the specific reactivity of fetal cells to maternally produced antibodies that **do not** bind to maternal blood cells. In fact, the skilled artisan reading Simons would conclude that Simons teaches away from the instant claimed methods by leading the skilled artisan to identify and utilize antibodies that bind to maternal antigens and not fetal

antigens, in contrast to the instant methods utilizing antibodies that bind to fetal cell antigens **and not** to maternal antigens.

The Action rejects the instant claims over the combination of Simons with either Warwick or Bussel, which are said to teach, "maternal antibodies that are specific for and bind to paternally-inherited fetal antigens." As the principle of operation of the method utilized by Simons is completely opposite to the principles of operation utilized by Warwick and Bussel, Applicant submits that the combination of Simons with either Warwick or Bussel is improper and according to MPEP 2145 may not be used to support a rejection under 35 U.S.C. 103.

Claim 6 is rejected under 35 U.S.C. 103 as unpatentable over Simons in view of Warwick or Bussel and further in view of Tsang et al. (J. Immunol. Meth. 138:291-99, 1991, hereafter "Tsang"). The impropriety of combining Simons with Warwick or Bussel is discussed above. Tsang is merely asserted by the Action as teaching dissociating bound antibodies from their antigen matrix by elution with dissociation reagents. As the combination of Simons with either Warwick or Bussel is improper, and Tsang adds nothing to that combination other than antibody dissociation, Applicant submits that claim 6 is not properly rejected under 35 U.S.C. 103 over Simons in view of Warwick or Bussel and further in view of Tsang.

Claim 10 is rejected under 35 U.S.C. 103 as unpatentable over Simons in view of Warwick or Bussel and further in view of Sisson et al. (J. Immunol. Metho. 127:215-20, 1990). The impropriety of combining Simons with Warwick or Bussel is discussed above. Sisson is merely asserted by the Action as teaching protein A binding to the Fc portion of IgG. As the combination of Simons with either Warwick or Bussel is improper, and Sisson adds nothing to that combination other than protein A binding, Applicant submits that claim 10 is not properly rejected under 35 U.S.C. 103 over Simons in view of Warwick or Bussel and further in view of Sisson.

Applicant further submits that, in addition to the impropriety of combining the primary reference (Simons) with either Warwick or Bussel, the Action has also failed to establish a prima facie case of obviousness. (MPEP §2142) None of Simons, Warwick, Bussel, Tsang or Sisson would have led the skilled artisan to believe that fetal cells could be identified or separated using complexes between maternal antibodies and paternally inherited fetal cell antigens on fetal cells. Simons says absolutely nothing about complexes between maternal antibodies and fetal antigens,

and in fact teaches away from the use of such complexes by leading the skilled artisan to utilize antibodies that bind to maternal antigens and not fetal antigens to separate fetal cells from maternal cells. Neither Warwick nor Bussel disclose the detection of maternal antibodies bound to fetal cells to identify or enrich the fetal cells. Neither Tsang nor Sisson is relevant to the existence of maternal antibody-fetal cell complexes. None of the cited prior art, alone or in combination, contains any teaching or suggestion to identify or separate fetal cells by looking for maternal antibody-fetal cell complexes.

For the reasons discussed above, Applicant submits that the pending claims are not properly rejected under 35 U.S.C. 103 over Simons in view of Warwick or Bussel and further in view of Tsang or Sisson. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant submits that the pending claims are in condition for allowance. An early decision to that effect is respectfully requested.

Respectfully submitted,

Date: March 24, 2008

By: /Richard A. Nakashima/
Richard A. Nakashima
#42,023
Phone: 303-447-7728